Adequacy of dialysis: trace elements in dialysis fluids

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Abstract. A number of considerations suggest that trace element disturbances might occur in dialysed patients. These must at least in part be ascribed to the dialysis treatment itself during which these constituents may either be transferred to or removed from the patient.

Tap water must be considered as the main source of dialysate trace metal contamination. These can adequately be removed during water treatment provided that, in addition to softening and deionization, reverse osmosis is available. However, even in the presence of the latter devices the possibility of serious contamination of the dialysis fluids leading to either chronic or acute intoxications still exists. The addition of chemical concentrates may also contribute to the increased concentrations of a number of trace metals. The toxic effects of aluminium in dialysis patients are well known and at the present time the element is still responsible for the greater part of trace metal-related problems in dialysis patients. Hence, the need for regular monitoring of aluminium cannot be ruled out at present. Strategies for diagnosis and treatment of aluminium overload have been updated. Recent studies demonstrated the efficacy of low desferrioxamine doses in diagnosis and treatment of aluminium overload, and optimal schedules for administration of the chelator and duration of treatment have been presented.

Recently, in an epidemiological survey serum silicon concentrations in dialysis patients were found to be increased up to 100-fold compared to subjects with normal renal function. Moreover, it was noted that silicon concentrations in the dialysis population differ from one centre to another and that increased levels are due to either the use of silicon-contaminated dialysis fluids or an increased oral intake of the element originating from a high silicon content in the drinking water. Besides aluminium and silicon, a transfer towards the patients during dialysis has also been reported for a number of other elements including copper, zinc, nickel, strontium and chromium. The possible consequences of dialysate contamination with these elements will briefly be dealt with in the present paper.

In contrast to trace metal accumulation, removal of trace metals during dialysis may at least in part contribute to the relative deficiency of particular essential elements. Selenium deficiency has repeatedly been observed. In view of the element’s well-known essential role in glutathion peroxidase activity and the association of its deficiency with the development of some malignant diseases, further studies on the clinical impact of decreased serum selenium in dialysis patients are worthwhile.

In conclusion, trace metal dialysate contamination/depletion may contribute to the disturbed trace element concentration in dialysis patients. Aluminium accumulation is still an important problem in clinical nephrology. The clinical importance of the accumulation/deficiency of trace elements other than aluminium is not yet fully understood and deserves further investigation.

Key words: trace elements; dialysis fluid; contamination; depletion; toxicity

Introduction

In patients with uraemia trace element disturbances might occur due to: (i) reduced renal function; (ii) proteinuria resulting in losses of protein-bound elements; (iii) alterations in gastrointestinal absorption because of alterations in e.g. vitamin D metabolism; (iv) the dialysis procedure per se. Indeed, according to the concentration gradient between the ultrafiltrable amount of a particular element in serum and its concentration in the dialysis fluid, some trace metals may be removed, whereas others present as contaminants in the dialysis solution could be transferred to the patient. Serious, acute as well as chronic intoxications and trace metal deficiencies have been reported [1,2].

Sources of dialysate trace element disturbances

Tap water may contain considerable amounts of trace metals and must in the absence of adequate treatment
be considered as the main source of trace metal contamination of the dialysis fluids. The acid rain-induced increase in the 'natural' concentration of some trace elements in water, particularly aluminium, mercury, manganese, zinc, nickel, lead and cadmium during the last decennia, is of particular interest [3]. Some domestic tap water contains aluminium in high concentrations either naturally or because the element has been added as a flocculant in the purification process. Also, concentrations of some elements in tap water may vary seasonally, e.g. silicon, or even on a day-to-day basis, e.g. aluminium.

Trace elements can adequately be removed during water treatment, provided that in addition to softening and deionization the water is treated by reverse osmosis (RO). However, carrying out these procedures does not necessarily imply the absence of these elements in the final dialysis fluid [2,4]. During our aluminium monitoring programme, dialysate contamination was observed in an Egyptian dialysis centre at the level of the heating tank of properly RO-treated water, which in turn resulted in a dialysate aluminium concentration as great as 85 µg/L and serious serum and bone aluminium accumulation [2]. In the summer of 1993 in a Spanish dialysis facility a major increase in plasma aluminium was noted which was due to an inadequate connection of the RO system [5]. Recently in a Portuguese centre clogging of the RO membranes of the water treatment installation resulting from the addition of extremely high amounts of flocculants resulted in an acute aluminium intoxication [2]. Also, aged RO membranes may inadequately retain elements such as silicon [4], which in dialysis patients may result in a significant accumulation of the element, and perhaps other trace elements in plasma. With regard to silicon, roller pump tubing has been demonstrated as another source of dialysate contamination with this element [6]. Acute nickel intoxication has been reported in dialysis patients treated with dialysis fluids contaminated from a nickel-plated stainless steel water heater tank [7]. Storage of water destined for the preparation of the dialysis fluids in a galvanized tank led to increased plasma and erythrocyte zinc [8] concentrations, while copper leached from the delivery system caused acute intoxication in a number of dialysis patients [9].

Whereas dialysate contamination with aluminium due to leakage from Redy sorbent cartridges [10] and aluminium anodes against boiler corrosion [11] has now disappeared, the control of added commercial salts appears cumbersome, and besides aluminium, identification of other contaminating elements these additives that might be responsible for pathological effects in dialysis patients is warranted. In this respect, Padovese et al. [12] demonstrated that dialysis fluids used for CAPD, HD or HF may contain trace metals in various concentrations depending on the chemical composition of the salts used to prepare the final dialysis fluid. They demonstrated that for a series of trace elements, including gold, barium, gallium, thallium, vanadium, nickel and chromium, the weekly exposure via the dialysis fluid appeared to be 50- to 120 000-fold greater than the estimated amount absorbed via the diet. In this context, our findings in a recent multicentre survey [4] demonstrating the addition of concentrates to result in dialysis fluids with silicon concentrations as great as 23 000 µg/L are of particular interest. Significant increases in fluoride concentration in plasma from patients with renal impairment undergoing chronic haemodialysis have also been observed when fluoridated water was used to prepare the dialysis fluids [13].

Whether the type of the dialysate, i.e. bicarbonate vs acetate, significantly influences the trace metal concentration and subsequent trace metal disturbances is not yet clear. It might be anticipated that under certain conditions trace elements used in plasticizers or alloys, such as mercury, iron, cadmium, tin and chromium, could be introduced into the dialysis fluid and thus transferred to the patient, resulting in acute or chronic intoxication.

On the other hand, as a consequence of an efficient water purification process, the subsequent ultra-low dialysate levels of a number of trace elements may lead to deficiency of some essential elements [14].

Trace element exchange during dialysis

The driving force for the transfer of trace elements during dialysis is the gradient between their concentration in the dialysis fluid and the free diffusible fraction in the blood compartment. As a consequence, with highly protein-bound elements, even low concentration of these substances in the dialysis fluid may result in a transfer of the element across the dialysis membrane. Hence, in dialysis patients having a serum aluminium around 20 µg/L, 80-90% of which is protein bound, there might be a transfer to the systemic circulation at aluminium levels in the dialysis fluid as low as 5 µg/L. Indeed, when comparing serum aluminium levels in patients from different centres, we recently noted that in the presence of a comparable Al(OH)₃ intake, the use of dialysis fluids with an aluminium concentration as low as 9 µg/L resulted in a significantly greater serum aluminium, compared to when patients were treated with dialysis fluids containing the element at concentrations <2 µg/L (Figure 1). In addition to aluminium, copper, zinc, nickel and a number of other trace metals are also bound to large plasma molecules. Here, any concentration of these elements in the dialysis fluid would also result in their transfer to the patient. A transfer towards the patient has also been noted in the presence of relatively low dialysate strontium [15] and chromium levels [16]. Even in the case of silicon, which in the serum of dialysis patients is present at concentrations 100- to 1000-fold greater than aluminium, as a free diffusible non-protein-bound low molecular weight compound, a transfer of the element towards the patient has been observed. Indeed, in some dialysis centres, dialysate silicon concentrations as great as 25 000 µg/L have been noted resulting in a
significant intra-dialytic accumulation of the element [4].

In contrast to this, low dialysate concentrations of a number of elements, e.g. boron [15], fluoride [13], selenium [14] and vanadium [17], may result in an adequate intra-dialytic removal of these components which in turn may result in deficiency of some essential elements [14], e.g. selenium.

Consequences of trace element disturbances in dialysis patients

Aluminium

The harmful effects of aluminium accumulation in dialysis patients have been well documented during the last decades. Aluminium overload has been implicated in the pathogenesis of several clinical disorders of the musculoskeletal, central nervous, and haematological systems [18]. Typical aluminium overload is rarely seen today. The issue, however, has switched towards more subtle disorders at the level of the parathyroid function and bone turnover, resistance to erythropoietin therapy and anaemia [19]. Hence, aluminium accumulation remains a problem in nephrology. Moreover, the risk for acute intoxications should always be considered (Table 1). Therefore, regular monitoring of aluminium levels of the water at all steps of the water purification process, of dialysis fluids and of serum aluminium remains necessary to detect dialysis centres and patients at risk for aluminium overload. In general, dialysate aluminium should not exceed 3 μg/l, and serum aluminium should remain less than 30 μg/l [20]. Further diagnosis of aluminium overload/aluminium-related bone disease is made by means of the low dose (5 mg/kg) desferrioxamine (DFO) test [20]. With regard to the treatment of aluminium overload/intoxication, it is worth noting that the use of a low aluminium dialysate may help to reverse aluminium-related diseases. However, it is ineffective to remove the element from its tissue stores. Here, aluminium chelation therapy using DFO at low doses (5 mg/kg) following well-standardized strategies and DFO administration schedules should be initiated [21].

Silicon

Silicon levels in dialysis patients are markedly increased. Besides renal insufficiency this must be ascribed to the oral intake of the element via silicon-containing drinking water and the use of silicon-contaminated dialysis fluids. Recently, in a multicentre study, we reported silicon contamination of the dialysis...
earlier reports suggesting an effect of the element on deserves further investigation, particularly in view of other types of renal osteodystrophy, a finding which

Interestingly, strontium levels were significantly greater ratio in dialysis patients to be significantly increased. The distribution
diagnosis of RO water in collection tank (85 µg/l)
Serum Aif: 119 ± 99 µg/l
Bone biopsies (n=6): 111 ± 116 µg/g wet weight
Portugal (1993) [21]
Dialysate contamination due to improper water
treatment. 11 patients died within 2 weeks
Spain (1993) [5]
Dialysate aluminium intoxication due to an inadequate connection of RO system
Serum Aif: from 31.9 ± 4.6 to 147.3 ± 11.7 µg/l
Russia (1995)*
Improper water treatment
USA (1995) [34]
Epidemic aluminium intoxication caused by the use of electric pumps with aluminium housing
Serum Al > 100 µg/l in 59 out of 86 patients

* Personal communication.

fluid to be due to either the use of RO membranes that insufficiently retain the element during water treatment, or to the addition of concentrates containing high amounts of silicon. Interestingly, it was further noticed that inadequate silicon removal by the RO membrane in general went along with inadequate removal of aluminium, i.e. failure to reduce the water aluminium after RO to less than 2 µg/l. Therefore, as a general rule if an RO membrane leaks it should be discarded not only for silicon but also for aluminium and perhaps a number of other trace metals also. The clinical significance of increased silicon levels is not yet fully understood. Using liquid chromatography combined with atomic absorption spectrometry, we demonstrated the element to appear in serum as a non-protein-bound low molecular weight fraction [4].

Strontium
Plasma strontium of patients treated by haemodialysis is reported to be increased [15]. Recent findings of our group do indicate that plasma strontium levels in dialysis patients are centre dependent and may vary from normal up to a 20-fold increase. The distribution of the element is similar to that of calcium, which means that 99% of the body burden is deposited in bone [22]. Compared to subjects with normal renal function we recently noted the bone strontium/calcium ratio in dialysis patients to be significantly increased. Interestingly, strontium levels were significantly greater in subjects with dialysis osteomalacia compared to all other types of renal osteodystrophy, a finding which deserves further investigation, particularly in view of earlier reports suggesting an effect of the element on bone metabolism and inhibition of the synthesis of 1,25-dihydroxycholecalciferol [23].

Selenium
Blood selenium in dialysis patients are frequently lower than in controls. This is due to a deficient dietary intake by the patients and/or losses through dialysis membranes [14]. Selenium plays an important role in glutathione peroxidase activity, an enzyme that protects membrane lipids and other cellular and extracellular components from oxidative damage [24]. A relationship has been found between selenium deficiency and the incidence of malignant diseases [25]. In view of this, some workers have recommended oral supplementation of the element to dialysis patients [14,26] which results in a significant increase in glutathione peroxidase activity [14]. More recently, selenium supplementation to haemodialysis patients resulted in a progressive increase in T-cell response to phytohaemagglutinin and in delayed-type hypersensitivity in the absence of severe side effects [26].

Others
Chromium may also enter the body via the dialysis fluid. We (unpublished observations) as well as others [16] noted serum chromium concentrations to be increased up to 20-fold compared with those observed in subjects with normal renal function. The potential of the element, particularly in its hexavalent state, to act as a carcinogenic substance is well known. Whether the increased levels in the dialysis population are of clinical significance is not yet clear, nor is it elucidated if the increased serum chromium in these patients are accompanied by an increased body burden of the element. In view of the latter, it is worth mentioning that in an ongoing study by our group investigating bone trace element content in end-stage renal failure, bone chromium in dialysis patients was significantly increased compared to subjects with intact renal function. The accumulation of the element in bone, however, could not be associated with the development of a particular type of renal osteodystrophy.

Although there are still some discrepancies in the literature regarding zinc levels in dialysis patients, most studies have found decreased concentrations of the element in serum and muscles while in bone and other tissues concentrations seem to be normal or even increased, suggesting translocation of the element in uraemia [1]. The dialysis treatment itself seems to have little or no effect on the serum zinc concentrations. Zinc deficiency in uraemic patients has been associated with anorexia and disturbances in taste and sexual performance [27]. More recently, a correlation was noted between decreased plasma zinc and erythrocyte superoxide dismutase levels [28].

Acute copper intoxication characterized by haemolysis, leucocytosis, metabolic acidosis, and gastrointestinal symptoms has been described in a number of dialysis patients [9]. Copper levels in serum of dialysis

Table 1. Aluminium intoxications: still a problem in nephrology?

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Details of intoxication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>1987-1990</td>
<td>Improper water treatment in 2 dialysis centres</td>
</tr>
<tr>
<td>Serum Aif:</td>
<td>78 ± 37</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>1993</td>
<td>Serum Aif: 83 ± 43 µg/l</td>
</tr>
<tr>
<td>Egypt</td>
<td>1992</td>
<td>Contamination of RO water in collection tank (85 µg/l)</td>
</tr>
<tr>
<td>Serum Aif:</td>
<td>119 ± 99</td>
<td></td>
</tr>
<tr>
<td>Paraguay</td>
<td>1991</td>
<td>No RO-treated water. Serum Aif: 83 ± 43 µg/l</td>
</tr>
<tr>
<td>Portugal</td>
<td>1993</td>
<td>Dialysate contamination due to improper water treatment. 11 patients died within 2 weeks</td>
</tr>
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<td></td>
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<td>Russia</td>
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<td>Improper water treatment</td>
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patients tend in general to be lower than normal. However, as for zinc, the element’s deficiency seems not to be due to the dialysis treatment itself. Here, loss of the element into the peritoneum is possible [29]. The effect of copper deficiency is not fully understood. The element is required for lysyl oxidase activity which is necessary for cross-linking of collagen. Its deficiency has been associated with growth retardation and anaemia [29]. Also in dialysis patients a correlation has been demonstrated between serum copper and superoxide dismutase activity [28].

Acute nickel intoxication during dialysis in a particular dialysis centre was accompanied by nausea, headache, vomiting, and weakness [7]. Nickel is an essential trace element shown to activate many enzymes [30]. The clinical importance of chronically elevated nickel concentrations originating from dialysis fluid contaminated by the addition of nickel-containing chemical concentrate is not yet elucidated, and further studies are in progress to test whether or not chronically increased concentrations of the element are accompanied by unrecognized symptoms of chronic intoxication [31].

The consequences of moderate fluoride accumulation are not yet known and are probably of little importance [13]. In some dialysis centres, however, fluoride accumulation has been associated with an increased incidence of osteomalacia. Although it has not been directly studied, it has been suggested that fluoride, like silicon, may decrease aluminium absorption since both elements may form tight complexes with each other [32].

Boron levels are about 5-fold increased in dialysis patients. In the presence of a low boron dialysate, serum levels decrease during dialysis, however they remain statistically higher than in subjects with normal renal function. To the best of our knowledge, no studies have been performed that, following studies in the chick, have demonstrated a linkage of the element with vitamin D metabolism in humans [33].

The status of vanadium in dialysis patients is at present not clearly established, however in general blood vanadium levels are elevated in chronic renal failure; notwithstanding, an interdialytic decrease of vanadium has been reported [17]. Also, a positive correlation between serum vanadium and systolic blood pressure has been reported [17].

Conclusions

Trace element content of dialysis fluids may contribute significantly to disturbed trace element levels in dialysis patients. Aluminium accumulation is still a problem in nephrology and acute intoxications with the element cannot be excluded. Although to a lesser extent, the possibility of acute as well as chronic intoxications of a number of trace elements others than aluminium also exists. Therefore, dialysate trace metal content should be checked regularly. The role of strontium in the development of osteomalacia, the clinical importance of increased silicon levels, as well as the issue of decreased selenium levels deserve further investigation.

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References

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